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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
FALK, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/03/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/656,935	BLUSZTAJN ET AL.	
	Examiner	Art Unit	
	Anne Falk	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *1-6,8,10,13,15 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-16* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: .

DETAILED ACTION

The response filed August 9, 2002 (Paper No. 12) has been entered.

Claims 1-16 are pending in the instant application.

Applicants' election with traverse, of Group VII, Claims 7, 9, 11, 12, and 14, in Paper No. 12 is acknowledged. The elected invention is directed to a method for *in vivo* differentiation or *in vivo* upregulation of particular genes. The traversal is on the grounds that the inventions of Groups VII and VIII are related in that they are both drawn to methods comprising BMP-9, for the treatment of patients in need of differentiating or treatment of cholinergic neurons. Applicants assert that a search of Groups VII and VIII would overlap and there would not be a serious burden in examining the groups together. This is not found persuasive because the method of the invention of Group VII is directed to protein therapy and the method of the invention of Group VIII is directed to cell therapy. Thus, an examination of the invention of Group VIII would require consideration of the issues involved in transplantation technology, whereas examination of the invention of Group VII would not. Methods of protein therapy and methods of cell therapy are different methods requiring different starting materials, different modes of operation, and produce different effects. The method of the invention of Group VII requires as starting materials a BMP-9-containing composition and a patient in need of cholinergic neurons, whereas the method of the invention of Group VIII requires as starting materials embryonic forebrain basal cells and a patient having Alzheimer's disease or malfunctioning cholinergic neurons. Methods of cell transplantation therapy have a substantially different and distinct mode of operation from methods of protein therapy and produce different effects at the cellular/biochemical level and typically at the level of clinical symptoms as well. Methods of cell transplantation requires consideration of issues not relevant to and not required for methods of protein therapy. Furthermore, a search for a method of protein therapy would not turn up art relating to a method of cell therapy, and vice versa. Therefore, additional searching would be required to

cover the inventions of both Groups VII and VIII. Because the searches are not coextensive and because the issues involved are substantially different, a search and examination of both inventions in one application would constitute a serious burden on the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-6, 8, 10, 13, 15, and 16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Applicant timely traversed the restriction requirement in Paper No. 12.

Accordingly, Claims 7, 9, 11, 12, and 14 are examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 7, 9, 11, 12, and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification asserts that compositions containing BMP-9 protein can be used to treat Alzheimer's disease (AD) and amyotrophic lateral sclerosis(ALS) (p. 2, lines 11-21). The specification further asserts that compositions containing BMP-9 protein can be used in the treatment of conditions exhibiting a degeneration of cholinergic neurons (p. 6, lines 12-15). The teachings of the specification are limited to analysis of embryos injected intracerebroventricularly with BMP-9 (Example I, pages 9-10), analysis of the pattern of expression of BMP-9 mRNA during mouse development (Example II, pages 10-13), and studies of the effect of BMP-9 on cells in culture (Examples II-VIII, pages 10-19). The

specification does not provide any working examples with regard to treatment of a diseased animal by administration of a BMP-9 composition.

The nature of the invention relates to treatment of patients having a variety of deficits in cholinergic neurons or in the expression of genes that affect the development and function of cholinergic neurons. The claims are broad in scope, encompassing a wide variety neurodegenerative diseases.

The specification fails to provide an enabling disclosure for the treatment of patients having a variety of diseases relating to malfunctioning or degenerating cholinergic neurons or motor neurons because in the absence of specific guidance, protein therapy is unpredictable. The art teaches that Alzheimers disease is a complex disease, arguably one of the most intractable of all major medical disorders. Specifically, Patel et al. (1995) states at page 81, column 1, paragraph 3, "[t]o date, there is neither a clear understanding of the origin and pathophysiology of AD nor an animal model of the illness." This is evidence of the extreme difficulty and unpredictability in treatment of AD. While the existing animal models have some of the features of AD, none of these models exhibit all the essential features of the human disease. Notably, in animal models, amyloid plaques are not accompanied by neurofibrillary tangles, both hallmarks of the disease. See The 1999 Progress Report on Alzheimer's Disease which states that amyloid plaques and neurofibrillary tangles are hallmarks of AD (p. 5, paragraph 5). Despite intensive effort on the research front, there are currently no effective treatments for Alzheimer's disease. A wide variety of therapeutic strategies for treating AD is being pursued. The major categories of these strategies are collected in Table 1 of Patel et al. (p. 82). Of particular relevance for this inquiry is the subcategory "Cholinergic Drugs." Patel notes the unpredictability of using various drugs to improve cognition in AD patients. Patel et al. state that the search for an effective cognition enhancing therapy for AD has so far proved to be elusive (p. 90, column 1, paragraph 2). In 1999, the National Institute on Aging reported that scientists do not yet fully understand what causes AD (Progress Report on Alzheimer's Disease, p. 7, paragraph 5) The instant specification does not provide any

working examples of the claimed invention and there is no teaching of how the data presented in the specification can be used to determine an effective amount of a BMP-9 composition for treating AD or any other neurodegenerative disorder. Further the specification does not provide specific guidance regarding a mode of administration that would produce a therapeutic effect in patients.

Given that specific treatment effects cannot be predictably achieved by merely administering a BMP-9 composition to a patient, specific guidance must be provided in the disclosure to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

In view of the limited guidance in the specification, the lack of applicable working examples, the unpredictability in the art of therapeutic strategies for neurodegenerative disorders, the broad scope of the claims, and the lack of specific guidance regarding how to use a composition comprising a BMP-9 protein therapeutically to treat a wide variety of neurodegenerative disorder, particularly ALS and AD, undue experimentation would have been required for one skilled in the art to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 9, 11, 12, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7, 9, 11, and 12 are indefinite because they depend from claims directed to non-elected subject matter.

Claim 7 is indefinite in its recitation of "differentiating cholinergic neurons" because it is unclear what the cholinergic neurons differentiate into.

Claim 7 is indefinite because there is no conclusory statement indicating that differentiation has occurred. The preamble recites "[a] method for differentiating cholinergic neurons in a patient" but the method only requires administering a BMP-9 composition, and does not require that said administration actually effect differentiation.

Claim 9 is indefinite because there is no conclusory statement indicating that any treatment is effected. The preamble recites "[a] method for treating degenerating and/or malfunctioning cholinergic neurons in a patient" but the method only requires administration of a BMP-9 composition, and does not require that said administration actually produce a treatment effect.

Claim 11 is indefinite in its recitation of "a patient in need of some administering a composition" because the phrase is grammatically incorrect and it is unclear what is being administered and what it is that the patient is in need of.

Claim 11 is indefinite because there is no conclusory statement indicating that upregulation of a choline acetyltransferase gene actually occurs. The preamble recites "[a] method for upregulating genes for choline acetyltransferase" but the method only requires administration of a BMP-9 composition, and

does not require that said administration actually produce upregulation of the genes for choline acetyltransferase.

Claim 12 is indefinite because there is no conclusory statement indicating that upregulation of vesicular acetylcholine transporter actually occurs. The preamble recites "[a] method for upregulating vesicular acetylcholine transporter" but the method only requires administration of a BMP-9 composition, and does not require that said administration actually produce upregulation of vesicular acetylcholine transporter.

Claim 14 is indefinite because there is no conclusory statement indicating that any treatment is effected. The preamble recites "[a] method for treating degenerating motor neurons in a patient" but the method only requires administration of a BMP-9 composition, and does not require that said administration actually produce a treatment effect.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk
ANNE-MARIE BAKER
PATENT EXAMINER